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Management Dockets, N/A
Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket 2005D-0021
International Conference on Harmonization Draft Guidance on Q8 Pharmaceutical Development

Dear Madam or Sir:

Enclosed please find comments from GlaxoSmithKline, including the key strategy issues and specific comments for the International Conference on Harmonization Draft Guidance on Q8 Pharmaceutical Development. These comments are presented for consideration by the FDA. The key strategy issues are presented first, with the specific comments presented in order by section and line number in the draft guidance.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this draft guidance. I am submitting the comments for this draft guidance by hardcopy. Therefore, you will receive this letter with two copies of comments.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

Mary Faye S. Whisler

Mary Faye S. Whisler, Ph.D.
Assistant Director
New Submissions, North America

2005D-0021

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Key Strategy Issues
This document represents a significant improvement on previous drafts, and we support it, with some relatively minor changes.
While we fully support all the concepts presented within the guideline, namely the application of scientific approaches and risk management to the development of a product and it's manufacturing process, we do have some concerns with the expectations of the regulatory agencies of the ICH regions with respect to their interpretation and implementation of some important aspects.
It should be acknowledged that the establishment of the "design space" will depend on many factors, and its size/dimensions will vary significantly from product to product for an individual company, and between companies.
While the focus of Q8, and in particular the design space concept, is on new drug products, the principles could be applied effectively to older products, e.g. to update manufacturing process information. However, it is important that this should not become mandatory, but should remain optional.
It is unclear on how the P2 document will be managed throughout the lifecycle of a product. The regional differences in EU, US and Japan (as well as other regions/countries accepting the ICH CTD-Q) in the regulatory processes and requirements for managing post-approval changes could make this difficult. Further clarification on this aspect is needed.
We support the recommendation that it is the level of knowledge gained, and not the volume of data submitted, that provides the basis for science-based submissions and their regulatory evaluation. While the presentation of product and process knowledge in a succinct and concise format may be a challenge for industry, the provision of extensive detail should be discouraged. We would hope that the regulators would adhere to this principle, and not request large volumes of data. This approach would be facilitated by a joint CMC assessor/inspector review, but is it is difficult to understand how this could be accommodated in the EU and Japan, with the current regulatory systems.
We are pleased that the establishment of the principle that a well defined design space could facilitate more flexible regulatory approaches.
We fully support the development of a Part 2 Annex to Q8, which provides guidance on individual dosage forms, provided this is in the form of "points to consider", rather than prescriptive requirements. We believe that the scope of the dosage forms covered should be consistent with Q6A, in the first instance. Decision trees, such as the selection of the sterilization process, could also be included in this annex. The inclusion of appropriate risk management examples to pharmaceutical development should also be considered for inclusion in the Part 2 Annex.

Item with Section and Line Number	Key Concerns with Explanation of Position	Proposed change
Section 2.2.2 Overages, Line 177	We believe that the statement on the use of overages is restrictive, and would recommend rewording.	Change the sentence to read: "Inappropriate use of overages, e.g. to compensate for poor formulation design, inadequate packaging or to extend shelf life, is not acceptable". This aligns better with the subsequent paragraph with its requirement that the justification/rationale for any overage be provided.
Section 2.2.3 Physicochemical and Biological Properties, Lines 191-195	The sentence "These could include formulation attributes such as ...." needs rewording. Some of these attributes, e.g. pH and osmolarity, are indeed formulation attributes. Others, such as particle size distribution, are primarily drug substance attributes, although we would look at granule size distribution.	Suggest changing text to read: "These could include formulation attributes such as pH, osmolarity, ionic strength, dissolution, re-dispersion, reconstitution, aggregation, rheological properties, globule size of emulsions biological activity or potency, and/or immunological activity along with drug substance properties such as particle size, distribution, particle shape lipophilicity and polymorphism."
Section 2.2.3, Physicochemical and Biological Properties, Lines 206-207	It is unclear what is meant by the statement "...acceptance criteria for polymorphism should be included in the drug product specification." Clarification is needed.	Suggest changing text to read: "For example, information could be provided from studies to investigate whether polymorphism of the drug substance is biologically relevant and this would determine whether polymorphism should be included in the drug product specification."
Section 2.4 Container Closure, Lines 272-274	The statement "This applies also to admixture or dilution of products e.g. product added to a large volume infusion container." is ambiguous and needs careful rewording.	Suggest changing text to read: "...e.g. product added to large volume infusion containers, where a representative sample of commonly used containers should be evaluated."

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Item with Section and Line Number	Key Concerns with Explanation of Position	Proposed change
Section 2.5 Microbiological Attributes, Lines 304-306	What does lowest mean in this context "The lowest specified concentration of ...?" Clarification on this point is needed.	Suggest changing text to read: "...effectiveness test. The concentration of antimicrobial preservative should take into account the chemical liability of the preservatives over the shelf life of the product along with the safety of the preservative system."
Section 2.6 Compatibility, Lines 314-316	The sentence "Where the label recommends dilution or mixing with food, prior to administration, appropriate compatibility studies should be described." needs clarification.	Suggest changing text to read: "...should be described, for example, compatibility of the formulation when dispersed in simulated gastric fluid in the fed state or simulated intestinal fluid in the fed state would be appropriate models. "
Section 3. Glossary, Lines 320-325	The definition of design space needs to be extended to make reference to importance of excipient characterization.	
Section 3. Glossary	A number of other terms associated with design space are being used in ongoing discussions around the concept. These include : Process specification Process signature Process trajectory.	The terms process specification, process signature, and process trajectory need to be defined in the final guideline.